

Remarks

Applicants have carefully considered this Application in connection with the Examiner's Action and respectfully request reconsideration of this Application in view of the following remarks.

Claims 1-12, 17-19, and 22-25 are pending, and claims 19, 23 and 24 have been withdrawn from consideration by the Examiner as being drawn to a non-elected species.

I. Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-12, 22 and 25 under 35 U.S.C. §103(a) as being obvious over Dietrich *et al.* ("Oxcarbazepine in Affective and Schizoaffective Disorders", *Pharmacopsychiatry*, 2001, 34, 242-250) in view of Almeida *et al.* ("Safety, Tolerability and Pharmacokinetic Profile of BIA-2-093, a Novel Putative Antiepileptic Agent, during First Administration to Humans," *Drugs R&D* 4(5): pp. 269-284, 2003). For the reasons discussed below, Applicants respectfully traverse the rejection.

The Applicants have surprisingly found that compounds used in the present invention are useful for the treatment of affective disorders, in particular bipolar disorder. (See Specification, page 2, third paragraph.)

The Examiner states that Dietrich teaches that oxcarbazepine as well as carbamazepine are effective in the treatment of acute mania and rapid cycling in patients with bipolar affective disorders, citing page 242, Table 1 and the conclusion of Dietrich. However, the Applicants would like to respectfully point out that on page 242, in Table 1 and in the conclusion of Dietrich there is no specific teaching with respect to bipolar disorders and oxcarbazepine. In fact, the only specific teachings in Dietrich with respect to oxcarbazepine and bipolar disorders are on page 244 with respect to a clinical trial investigating the prophylactic efficacy of oxcarbazepine in bipolar and schizoaffective patients, and on page 245 where a study is mentioned where oxcarbazepine and lithium were co-administered to a patient who had bipolar affective disorder. On page 244, Dietrich states that no valid conclusions could be drawn about the prophylactic effects of oxcarbazepine in bipolar patients. On page 245, Dietrich states that lithium and oxcarbazepine were combined without any adverse effects and that a steady clinical response without adverse reaction was observed in the patient

with bipolar affective disorder. There is therefore, no specific teaching in Dietrich with respect to the effectiveness of oxcarbazepine alone in treating bipolar disorders.

As the Examiner points out, Dietrich fails to specifically disclose eslicarbazepine acetate. As a result, there is no teaching or suggestion whatsoever in Dietrich that eslicarbazepine acetate would be useful for the treatment of any affective disorders, including bipolar disorders, either alone or in combination with any other active compounds.

The Examiner cites Almeida which describes a study conducted to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of eslicarbazepine acetate in healthy males. Almeida states that there were no clinically significant abnormalities in laboratory safety tests, vital signs, weight, physical examination or ECG reported and that the results provide a basis for further clinical trials with eslicarbazepine acetate. (See the Abstract of Almeida.) From this, the Examiner concludes that eslicarbazepine acetate is safe and well tolerated for human administration.

The Examiner also states that Almeida teaches that eslicarbazepine acetate is structurally different from carbamazepine and oxcarbazepine at the 10,11-position and that this molecular variation results in differences in metabolism, namely by preventing the formation of toxic epoxide metabolites and unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates without losing antiepileptic potency. (See Office Action, page 4, first paragraph.)

Almeida discloses eslicarbazepine acetate as an antiepileptic drug and does not suggest or teach that eslicarbazepine acetate is useful as anything other than an antiepileptic drug. (As the Examiner states on page 4 of the Office Action, the molecular variation of eslicarbazepine acetate from oxcarbazepine and carbamazepine results in differences in metabolism without losing antiepileptic potency.)

Nevertheless, the Examiner concludes that it would be *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted eslicarbazepine acetate as taught by Almeida for oxcarbazepine in the method of treating manic episodes of bipolar disorder as taught by Dietrich. (See Office Action, page 4, second paragraph.) The Examiner cites a variety of reasons why one of ordinary skill in the art would have been motivated to make the substitution and why one

of ordinary skill in the art would have had a reasonable expectation of success in treating manic episodes of bipolar disorder in a patient in need thereof by administering eslicarbazepine acetate, such as eslicarbazepine acetate being a derivative of oxcarbazepine, sharing a common structural core with oxcarbazepine, and being safe and well-tolerated for human administration.

In essence, the Examiner's argument for combining the references is that simply because eslicarbazepine acetate is a derivative of oxcarbazepine and appears to be safe to administer to humans, it would be obvious to substitute eslicarbazepine acetate for oxcarbazepine and to use eslicarbazepine acetate to treat manic episodes of bipolar disorder.

However, simply because a compound is a derivative of another compound and appears to be safe to administer to humans is not a sufficient basis for combining references. There must be some teaching or suggestion that would motivate one of ordinary skill in the art to combine the references as the Examiner has combined them.

In this case, Dietrich does not even mention eslicarbazepine acetate, much less teach or suggest that eslicarbazepine acetate would be useful to treat bipolar disorders, nor does it specifically teach the use of oxcarbazepine alone to treat bipolar disorders. As noted above, Almeida only teaches that eslicarbazepine acetate is an antiepileptic drug and does not teach or suggest that eslicarbazepine acetate is useful in the treatment of any affective disorder. In other words, neither reference has any teaching or suggestion that eslicarbazepine acetate would be useful in the treatment of bipolar disorders, and Dietrich does not specifically teach that oxcarbazepine alone would be useful in the treatment of bipolar disorders. Therefore, one of ordinary skill in the art would not have been motivated to combine the references as the Examiner has combined them and would not have had a reasonable expectation of success that eslicarbazepine acetate would be useful in the treatment of manic episodes of bipolar disorder at the time of the Applicants' invention.

As a result, neither Dietrich or Almeida, alone or in combination, teaches or suggests each and every element of Applicants' claimed invention in Claims 1-12, 22 and 25 as required to establish a *prima facie* case of obviousness under 35 U.S.C. §

103(a). Accordingly, the Applicants respectfully request that the rejection of Claims 1-12, 22 and 25 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

The Examiner has also rejected Claims 17 and 18 under 35 U.S.C. §103(a) as being unpatentable over Dietrich and Almeida as applied to Claims 1-12, 22 and 25 in view of Beasley *et al.* (US Patent No. 5,605,897). For the reasons discussed below, Applicants respectfully traverse the rejection.

Claims 17 and 18 are directed to combination treatment. The Examiner cites Beasley as teaching olanzapine as being useful in the treatment of bipolar disorder. The Examiner then concludes that it would have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have combined olanzapine as taught by Beasley with eslicarbazepine acetate in the method of treating manic episodes of bipolar disorder as taught by Dietrich and Almeida because both olanzapine and eslicarbazepine acetate are useful for treating bipolar disorder. (See Office Action, page 5, last two paragraphs.)

However, Dietrich and Almeida do not teach a method of treating manic episodes of bipolar disorder, and as set forth above, one of ordinary skill in the art would not have been motivated to combine Dietrich and Almeida as the Examiner has combined them. As set forth above, Dietrich does not even mention eslicarbazepine acetate, much less teach or suggest that eslicarbazepine acetate would be useful to treat bipolar disorders nor does it specifically teach the use of oxcarbazepine alone to treat bipolar disorders. As also noted above, Almeida only teaches that eslicarbazepine acetate is an antiepileptic drug and does not teach or suggest that eslicarbazepine acetate is useful in the treatment of any affective disorder. In other words, neither reference has any teaching or suggestion that eslicarbazepine acetate would be useful in the treatment of bipolar disorder, and Dietrich does not specifically teach that oxcarbazepine alone would be useful in the treatment of bipolar disorders. It is therefore incorrect to state that Dietrich and Almeida teach a method of treating manic episodes of bipolar disorder using eslicarbazepine acetate.

Since Dietrich and Almeida do not teach eslicarbazepine acetate in the treatment of manic episodes of bipolar disorder, the Applicants respectfully submit that the Examiner's basis for combining the references is improper. Furthermore, bipolar

disorders are only one of many diseases, disorders and conditions set forth in Beasley as diseases, disorders and conditions that allegedly could be treated with olanzapine. There is no experimental data in Beasley, either preclinical or clinical, that demonstrate that olanzapine is in fact useful in the treatment of bipolar disorders or that would lead one of ordinary skill in the art to select a bipolar disorder from the numerous diseases, conditions and conditions that Beasley alleges can be treated with olanzapine.

As a result, none of the references, either alone or in combination, teaches or suggests each and every element of Applicants' claimed invention in Claims 17 and 18, as required to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Accordingly, the Applicants respectfully request that the rejection of Claims 17 and 18 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

II. Conclusion

In view of the foregoing, Claims 1-12, 17-19, and 22-25 are in condition for allowance, and Applicants earnestly solicit a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Reply is respectfully requested.

Respectfully submitted,
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